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<b>(21) International Application Number:</b> PCT/CA93/00109 <b>(22) International Filing Date:</b> 18 March 1993 (18.03.93)  <b>(30) Priority data:</b> 854,406                      19 March 1992 (19.03.92)                      US  <b>(71) Applicant (for all designated States except US):</b> THE UNIVERSITY OF BRITISH COLUMBIA [CA/CA]; Research Administration, Room 331, IRC Building, 2194 Health Sciences Mall, Vancouver, British Columbia V6T 1W5 (CA).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only) :</b> BURTON, Albert, F. [CA/CA]; 297 Rodello Street, Comox, British Columbia V9N 4Z9 (CA). FREEMAN, Hugh, J. [CA/CA]; 2211 Wesbrook Mall, Vancouver, British Columbia (CA). MCGEER, Patrick, L. [CA/CA]; 4727 West 2nd Avenue, Vancouver, British Columbia (CA).		<b>(74) Agent:</b> OYEN, Gerald, O., S.; Barrigar & Oyen, #480-601 West Cordova Street, Vancouver, British Columbia V6B 1G1 (CA).  <b>(81) Designated States:</b> AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).  <b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> METHOD AND COMPOSITION FOR SUPPRESSION OF SIDE EFFECTS OF ANTI-INFLAMMATORY DRUGS  <b>(57) Abstract</b>  This invention pertains to the novel use of N-acetyl glucosamine to overcome or minimize the side-effects of anti-inflammatory agents by providing for the synthesis of essential human tissue components whose formation is inhibited by the action of these drugs. A method of minimizing adverse side effects in a human being who is being treated with anti-inflammatory agents comprising feeding the human being a therapeutic amount of N-acetyl glucosamine, and pharmaceutically acceptable carriers, on a periodic basis.		

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METHOD AND COMPOSITION FOR SUPPRESSION OF  
SIDE EFFECTS OF ANTI-INFLAMMATORY DRUGS

FIELD OF THE INVENTION

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This invention pertains to the novel use of N-acetyl glucosamine to overcome or minimize the side-effects of anti-inflammatory agents by providing for the synthesis of essential human tissue components whose formation is inhibited by the action of these drugs.

BACKGROUND OF THE INVENTION

Anti-inflammatory agents are the most widely used of medications, and include two main types: steroid and non-steroid. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently prescribed drugs and are used on a daily basis by 40 million people in North America alone. Corticosteroids are derived from the natural hormone, cortisol, which is essential for life, but whose many properties have been exploited for therapeutic purposes including its anti-inflammatory effects. Corticosteroids are frequently life-saving in more severe situations and are very effective in many diverse conditions. These include the suppression of the inflammatory response which is a common accompaniment of many human disorders, as well as suppression in humans of the immune response which is also considered to be responsible for many disorders which, among other effects, initiate inflammation.

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Corticosteroids inhibit most cellular processes thereby decreasing those which are harmful, but in long-term treatment - months or years - the slowing of synthetic processes results in deficiencies in many tissues. Corticosteroids inhibit protein synthesis which impairs growth and regeneration of tissues. Some of these effects can be at least partially overcome by modifications in treatment schedules and diet.

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Both corticosteroids and NSAIDs appear to owe their anti-inflammatory action largely to the inhibition of the synthesis of prostaglandins, which are regulatory substances formed in tissues and which modify function of many processes in various ways. Prostaglandins play a major role in initiating the inflammatory response so suppressing the synthesis of prostaglandins can be a desired effect. However, some processes which are essential for normal tissue function are also slowed by the inhibition of prostaglandin synthesis.

Corticosteroid treatment for many months can result in inhibition of the synthesis of vital substances thereby causing serious tissue defects. In joints, the formation of glycosaminoglycans such as hyaluronate, a major constituent, is impaired. This can lead to severe damage of joints, especially large joints such as the hip. Hyaluronate is 50 percent by weight composed of N-acetyl glucosamine (NAG). The supporting structures around blood vessels are also composed of NAG and related substances, and defective synthesis leads to vascular fragility and easy bruising.

A major side-effect of both corticosteroids and NSAIDs is decreased synthesis of the protective lining of the digestive tract. Especially in the case of NSAIDs, which are more commonly used, the development of ulcers in the lining of the stomach and the duodenum and of gastrointestinal bleeding is a major problem. About 5 percent of persons taking NSAIDs, mostly the elderly, suffer from such problems.

#### SUMMARY OF THE INVENTION

The invention pertains to a method of minimizing adverse side effects in a human being who is being treated with anti-inflammatory agents comprising feeding the human

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being a therapeutic amount of N-acetyl glucosamine on a periodic basis. The N-acetyl glucosamine can be ingested by the patient either alone, or with a pharmaceutically acceptable carrier, or with a corticosteroid or a non-steroidal anti-inflammatory drug.

The N-acetyl glucosamine can be fed to the human being on a daily basis. The dosage can be about 300 mg to about 10,000 mg, about 1,000 mg to about 6,000 mg or about 500 mg of N-acetyl glucosamine per day. The N-acetyl glucosamine can be incorporated in a pharmaceutically acceptable carrier. The N-acetyl glucosamine can be fed to the human being as required to restore the integrity of affected tissues in the body of the human being.

The invention is also directed to a composition useful for minimizing adverse side effects in a human being who is being treated with anti-inflammatory agents comprising N-acetyl glucosamine and a pharmaceutically acceptable carrier. The N-acetyl glucosamine can be present in the amount of about 300 mg to 10,000 mg, or about 1,000 mg to about 6,000 mg.

#### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

There are structures in many tissues of the body the synthesis of which are reduced by anti-inflammatory drugs. Such synthesis can be increased by provision of N-acetyl glucosamine without diminishing the anti-inflammatory action of the drugs.

N-acetyl glucosamine (NAG) is formed from glucosamine. NAG is then directly converted into other amino sugars in the human body. NAG is a key substance in the healthy function of constant tissue regeneration and replacement. We have found that the formation of NAG itself from glucosamine is the slow part of the overall

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amino sugar processing sequence. This necessitates the use of NAG, specifically, and not a de-acetylated form, or an oligomer.

5           N-acetyl glucosamine is more stable than glucosamine, is a neutral substance and is readily assimilated and utilized by tissues whereas most oligomers are not.

10           It is important to note that it is the availability of amino sugars which appears to limit the synthesis of these vital glycoproteins and glycosaminoglycans. When blood flow is thus arrested, an ulcer forms within an hour, illustrating dramatically the dynamic nature of these  
15           regeneration processes and the need for continual synthesis. The action of a drug, Proglumide, which protects against gastric erosion, has been attributed to the fact that it stimulates synthesis of glycoproteins and glycosaminoglycans (Umetsu, T. et al., European Journal of  
20           Pharmacology 1980, 69: 69-77).

20           We have found that N-acetyl glucosamine can be provided as an external human body source to provide for synthesis of essential tissue components when the synthesis of such components is inhibited by administration of anti-  
25           inflammatory agents. The synthesis of each component can be stimulated by NAG without interfering with the anti-inflammatory action of these drugs, both corticosteroids and NSAIDs.

30           Tissue defects in the digestive tract of human beings suffering food intolerance or food allergies have been found. These defects can be corrected to enable the mucosa in the tract to form a necessary barrier to transmission of food allergens and to maintain normal function.  
35           The mucosa tissue structure is rich in amino sugars derived from N-acetyl glucosamine and we have found that the

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availability of N-acetyl glucosamine is critical to its synthesis.

N-acetyl glucosamine (NAG) is an amino sugar, which is formed in all animal cells and is utilized for the synthesis of many cellular components. The biochemical process by which these components are made is similar in all cells although the end products differ depending upon the type of cell involved. Most of the end products are found outside the cells where they form sheaths which bind cells together, and are major structural components, as in the walls of blood vessels, and fill the spaces between cells, i.e. the interstitium. Amino sugars are found combined with other large molecules (macromolecules) of protein, lipid (fats) or other carbohydrates to form glycoproteins (GP), glycolipids (GL) and glycosaminoglycans (GAG). Glycoproteins have many functions, some circulate in the blood, others are anchored on the surface of cells, as are glycolipids. They can confer unique properties to the cell, for example, on the surface of red blood corpuscles there is a glycolipid which determines the blood groups A, B and O. The sole difference between these groups is the presence of a single amino sugar. Such remarkable specificity indicates that there is a "language" in which amino sugars are the "letters" analogous to the genetic code, by which biological information is recorded and put into action.

Each cell makes its own amino sugars and the process, as in the case of most biochemical synthesis, is regulated by the availability of the first member of the sequence, which in this case is glucosamine. Glucosamine is formed from the pool of sugars derived from glucose, blood sugar, and is acetylated to form N-acetyl glucosamine (NAG). NAG is the immediate precursor for two other amino sugars, N-acetyl galactosamine and N-acetyl neuraminic (sialic) acid. These amino sugars constitute about half

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the total weight of the GAG found in human tissues (References 1-7).

5 In the synthesis of these molecules, the availability of the substrate, amino sugars, is critical to proper function. We have discovered that although the formation and utilization of amino sugars takes place in all human cells independently, nevertheless an external source of amino sugar is readily taken up by the cells and  
10 is utilized by them for incorporation into the macromolecules. An external source of amino sugar, we have found, can provide for an adequate amount of substrate to satisfy cell demands which otherwise might be greater than the cells can meet.

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The interstitium is the space between the cells which contains the fibrous protein collagen ensheathed by glycosaminoglycan (GAG). The GAG absorbs very large quantities of water to form a gel-like material which resists  
20 compression thereby giving shape and firmness to the tissue. This material acts as a medium which regulates the passage of nutrients, etc., between the blood and the tissues, and also acts as a barrier, for example, to the spread of infection (Bert and Pearce).

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Mucous membranes are covered by a microscopically thin glycoprotein rich in sialic acid called the glycocalyx. In the gastrointestinal tract (GI), this microscopically thin layer is the ultimate barrier between the  
30 underlying tissue and the corrosive digestive juices. When the layer is damaged, erosion and ulceration of the underlying tissue occurs. If the blood supply to the upper GI is arrested for about 5 minutes, for example, it has been found that all synthetic processes cease, including formation of the glycocalyx, and an ulcer can be seen forming  
35 within an hour. This illustrates the dynamic nature of the biological processes in the human body. There are several



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hundred grams of amino sugar in the various tissue components of the body but the average life of a given molecule is only 3 days or so. There is thus a constant turnover of all molecules in the body, even in tissues such as bone, and a constant supply of substrates for synthesis is therefore required.

An important and novel feature of the present invention is that increased demands caused by injury such as food allergen injury can be placed upon cells which might strain their resources, and in this situation, an external supply of amino sugars is beneficial. In the gastrointestinal tract (GI), the rate of synthesis of the glycocalyx had been considered to be adequate in persons afflicted with Inflammatory Bowel Disease (IBD). However, in these persons, as in many situations where there is disease or injury, the turnover of cells is increased, perhaps as much as threefold. This creates a demand that is beyond what is considered normal. We have found that the incorporation of NAG into the intestinal mucosal tissue is three times greater in persons afflicted with IBD than in those who are not afflicted.

We have also found that in human placenta near term, the formation of glycosaminoglycan (GAG) is stimulated strongly by the steroid 17  $\alpha$ -hydroxyprogesterone (Burton et al.) which appears to function by increasing the synthesis of amino sugars. We have discovered that the same stimulation can be achieved merely by providing the appropriate amino sugars.

Others have shown that in chondrocytes, the cells which form cartilage, the presence of corticosteroids inhibits the formation of GAG. Supplying amino sugars largely overcame this inhibition (Fassbender).

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In a recent publication, the question of intestinal permeability in persons with Crohn's Disease, a form of IBD, was reviewed (Olaison et al.). It was found that these persons have greater than normal permeability of the GI tract which leads to the absorption into the bloodstream of substances normally excluded. This includes the substances which cause food sensitivities or food allergies. The condition is attributed to a defect in the mucosal barrier, the glycocalyx, and the intercellular cement composed of GAG. Even unaffected relatives of these patients have been found to have increased permeability (Hollander et al.) which supports the concept that some individuals have a genetic or constitutional defect which sets the stage for a spectrum of disorders ranging from mild to serious food intolerance to severe inflammatory lesions.

Various agents inhibit the formation of the mucosal barrier including ethanol, aspirin and other anti-inflammatory agents. Erosion and bleeding of the GI tract is a major side-effect of such drugs. An agent, proglumide, which protects against ulcer formation has been shown to stimulate the incorporation of NAG into mucosal glycocalyx and this is considered the reason for its effectiveness (Umetsu).

Inflammation is a common accompaniment of many forms of injury and is part of the body's defence and repair mechanism. Often, however, the inciting agent is such that the inflammation serves no protective purpose and in fact results in tissue damage causing pain and disability, as in arthritis.

The treatment of these conditions involves the use of anti-inflammatory drugs such as aspirin and of corticosteroids. These have great benefits. However, they have side-effects which are largely related to their

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slowing the formation of tissue structures such as GP and GAG which contain amino sugars.

There are, therefore, many situations where an external source of amino sugar can be beneficial. We have discovered that a good choice is N-acetyl glucosamine (NAG) which is a neutral compound, is stable, is very soluble, is tasteless, and is readily absorbed from the digestive tract. It circulates in the blood with a half-life about 4 hours and very little is excreted since it is a "committed metabolite" utilized exclusively for the synthesis of GP, GL, GAG in tissue components. An external supply is readily taken up and utilized by the human body and therefore has the potential to be of benefit in many situations where the synthetic processes are less than adequate to meet demands. NAG alone is capable of efficient utilization for these processes when taken by mouth.

#### Example 1

#### Case History - R.R.

R.R., male, 42, underwent surgery for Inflammatory Bowel Disease with partial removal of the colon. After the surgery, he continued to suffer rectal bleeding and ulceration of the mouth. He took aspirin and acetaminophen regularly for pain relief, and underwent surgery for hip replacement, due to hip degeneration from arthritis and administration of anti-inflammatory agents. He began taking NAG, 3 g per day, before the hip surgery and continued taking it at that rate during and after the surgery. He reported that the main immediate improvement he experienced was less fatigue and nausea, and a generally better feeling. However, he also noted after several weeks of NAG ingestion that there was a lessening of rectal bleeding, and a decrease in the development of mouth ulcers.

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R.R. then underwent surgery for complete removal of the colon. At the time, he stopped taking NAG. He again began to experience difficulties with intestinal discomfort and mouth ulcers. Subsequent to surgery for removal of the colon, he resumed taking NAG at a rate of 3 g per day and found that as before, it made him feel better and lessened the incidence of mouth ulcers.

In the period before colectomy, the evidence of decreased bleeding is of significance and is consistent with the discovery that NAG provides for the formation of essential tissue structures whose deficiency contributes to GI bleeding and oral cavity lesions.

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Example 2Case History - A.B.

A.B., male, 62, was taking aspirin at a rate of 325 mg per day. Gastrointestinal bleeding began suddenly after a time of taking such aspirin. Black stools (which indicate blood from internal bleeding) were accompanied by considerable fresh blood with every movement. Discomfort in the upper abdomen was felt.

A.B. began taking NAG at a dosage of 3-4 g per day, as soon as intestinal bleeding was observed. A.B. also continued to take aspirin. No other medication was taken, such as antacids. Bleeding began to decrease after 3 days of treatment and was completely gone in 4 days. Thirteen days after bleeding had started, A.B. visited a gastroenterologist who advised terminating the aspirin ingestion. The diagnosis was upper GI, probably duodenal bleeding, likely caused or aggravated by the aspirin. Blood tests indicated that haemoglobin fell from 142 to 109 g per litre, representing a loss of about 25% of blood volume. Subsequently, A.B. began to take NAG and after 4 weeks, the upper abdominal discomfort had disappeared

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completely. Aspirin consumption was resumed (without the physician's knowledge) but taken together with NAG, A.B. continues to be free of any GI symptoms after 4 months.

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## WHAT IS CLAIMED IS:

1. A method of minimizing adverse side effects in a human being who is being treated with anti-inflammatory agents characterized by feeding the human being a therapeutic amount of N-acetyl glucosamine on a periodic basis.  
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2. A method according to claim 1 wherein the N-acetyl glucosamine is fed to the human being on a daily basis.  
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3. A method according to claim 1 wherein the human being is fed about 300 mg to about 10,000 mg of N-acetyl glucosamine per day.  
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4. A method according to claim 1 wherein the human being is fed about 1,000 mg to about 6,000 mg of N-acetyl glucosamine per day.
- 20 5. A method according to claim 1 wherein the human being is fed about 500 mg of N-acetyl glucosamine per day.
6. A method according to claim 3 wherein the N-acetyl glucosamine is incorporated in a pharmaceutically acceptable carrier.  
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7. A method according to claim 1 wherein the N-acetyl glucosamine is fed to the human being as required to restore the integrity of affected tissues in the body of the human being.  
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8. A method according to claim 1 wherein the anti-inflammatory agent is a corticosteroid.
- 35 9. A method according to claim 1 wherein the anti-inflammatory agent is a non-steroidal anti-inflammatory drug.

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10. A composition useful for minimizing adverse side effects in a human being who is being treated with anti-inflammatory agents comprising N-acetyl glucosamine and a pharmaceutically acceptable carrier.

11 A composition according to claim 10 wherein the N-acetyl glucosamine is present in the amount of about 300 mg to 10,000 mg.

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12. A composition according to claim 10 wherein the N-acetyl glucosamine is present in the amount of about 1,000 mg to about 6,000 mg.

13. A composition for minimizing adverse side effects in a human being who is being treated with anti-inflammatory agents comprising a therapeutic amount of N-acetyl glucosamine, and a therapeutic amount of an anti-inflammatory agent.

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14. A composition according to claim 13 wherein the anti-inflammatory agent is selected from the group consisting of corticosteroids and non-steroidal anti-inflammatory agents.

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15. A composition according to claim 14 wherein the N-acetyl glucosamine is present in the amount of about 300 mg to about 10,000 mg.

16. A composition according to claim 15 wherein the N-acetyl glucosamine is present in the range of about 1,000 mg to about 6,000 gm.

17. A composition according to claim 15 wherein the N-acetyl glucosamine is present in the amount of about 500 mg.

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18. A composition according to claim 15 wherein the N-acetyl glucosamine is associated with a pharmaceutically acceptable carrier.

5 19. A composition useful for minimizing adverse side effects in a human being who is being treated with anti-inflammatory agents comprising N-acetyl glucosamine, a pharmaceutically acceptable carrier, and an anti-inflammatory agent.

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20. A composition useful for minimizing adverse side effects in a human being who is being treated with corticosteroids comprising N-acetyl glucosamine, a pharmaceutically acceptable carrier, and an anti-inflammatory agent.

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21. A composition according to claim 19 wherein the anti-inflammatory agent is non-steroidal.



## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/CA 93/00109

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) <sup>6</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 A61K31/70		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
Int.Cl. 5	A61K	
Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched <sup>8</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b>		
Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
X	EP,A,0 154 523 (RAINSFORD, KIM DRUMMOND) 11 September 1985 see page 2, paragraph 2; claim 3	1-21
X	BIOCHEMICAL PHARMACOLOGY vol. 29, no. 9, 1980, pages 1281 - 1289 K. D. RAINSFORD ET AL. 'Biochemical gastroprotection from acute ulceration induced by aspirin and related drugs' see table 2	1-21
X	EP,A,0 372 730 (THE UNIVERSITY OF BRITISH COLUMBIA) 13 June 1990 see claims 1-3	10-12
X	EP,A,0 234 207 (SPECK, ULRICH, DR) 2 September 1987	10-12
<p><sup>10</sup> Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
01 JULY 1993		22.07.93
International Searching Authority		Signature of Authorized Officer
EUROPEAN PATENT OFFICE		TZSCHOPPE D. A.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	EP,A,0 013 783 (THE AUSTRALIAN NATIONAL UNIVERSITY) 6 August 1980 see page 2, paragraph 4 -----	1-21

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.**

CA 9300109  
SA 72360

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.  
The members are as contained in the European Patent Office EDP file on  
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01/07/93

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